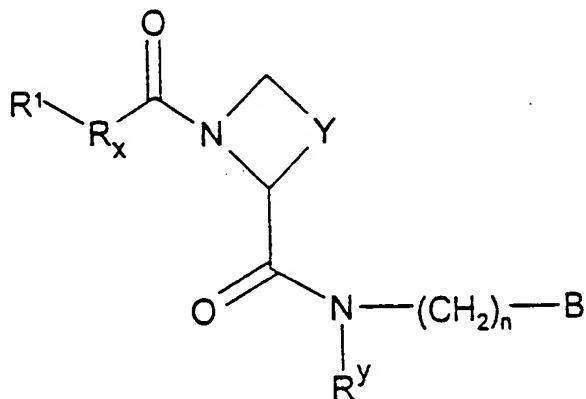


AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

1 (currently amended). A compound of formula I,



wherein

R¹ represents H, C₁₋₄ alkyl (optionally substituted by one or more substituents selected from cyano, halo, OH, C(O)OR^{1a} or C(O)N(R^{1b})R^{1c}) or OR^{1d};

R^{1d} represents H, C(O)R¹¹, SiR¹²R¹³R¹⁴ or C₁₋₆ alkyl, which latter group is optionally substituted or terminated by one or more substituent selected from OR¹⁵ or (CH₂)_qR¹⁶;

R¹², R¹³ and R¹⁴ independently represent H, phenyl or C₁₋₆ alkyl;

R¹⁶ represents C₁₋₄ alkyl, phenyl, OH, C(O)OR¹⁷ or C(O)N(H)R¹⁸;

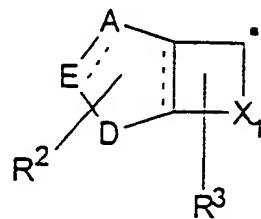
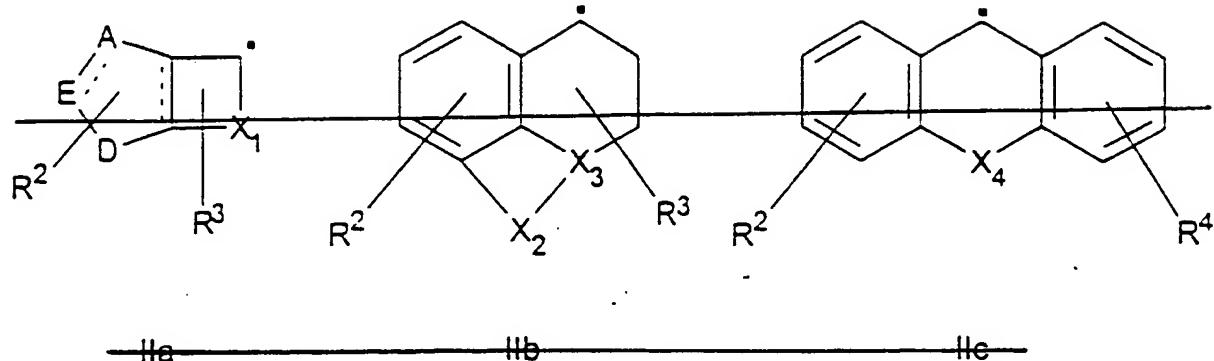
R¹⁸ represents H, C₁₋₄ alkyl or CH₂C(O)OR¹⁹;

R¹⁵ and R¹⁷ independently represent H, C₁₋₆ alkyl or C₁₋₃ alkylphenyl;

R^{1a}, R^{1b}, R^{1c}, R¹¹ and R¹⁹ independently represent H or C₁₋₄ alkyl; and

q represents 0, 1 or 2;

R_x represents a structural fragment of formula IIa, IIb or IIc,



IIa

wherein

the dotted lines independently represent optional bonds;

A and E independently represent Θ or S , CH or CH_2 (as appropriate), or N or

$N(R^{21})$ (as appropriate);

D represents $-CH_2-$, O , S , $N(R^{22})$, $-(CH_2)_2-$, $-CH=CH-$, $-CH_2N(R^{22})-$,

$-N(R^{22})CH_2-$, $-CH=N-$, $-N=CH-$, $-CH_2O-$, $-OCH_2-$, $-CH_2S-$ or $-SCH_2-$;

X₁ represents C₂₋₄ alkylene; C₂₋₃ alkylene interrupted by Z; -C(O)-Z-A¹-Z-A³;

-Z-C(O)-A¹-CH₂-C(O)-A¹-Z-C(O)-Z-A²-CH₂-Z-C(O)-A²;

-Z-CH₂-C(O)-A²-Z-CH₂-S(O)_m-A²-C(O)-A³-Z-A³; or A³-Z;

X₂ represents C₂₋₃ alkylene, C(O)-A⁴ or A⁴C(O);

X₃ represents CH or N;

X₄ represents a single bond, O, S, C(O), N(R²³), -CH(R²³)-,

-CH(R²³)-CH(R²⁴) or C(R²³)=C(R²⁴);

A¹ represents a single bond or C₁₋₂ alkylene;

A² represents a single bond or CH₂;

A³ represents C₁₋₃ alkylene;

A⁴ represents C(O) or C₁₋₂ alkylene;

Z represents, at each occurrence, Θ, S(O)_m or N(R²⁵);

R² and R⁴ independently represent one or more optional substituents

selected from C₁₋₄ alkyl, C₁₋₄ alkoxy (which latter two groups are optionally substituted by one or more halo substituent), methylenedioxy, halo, hydroxy, cyano, nitro, S(O)₂NH₂, C(O)OR²⁶, SR²⁶, S(O)R^{26a}, S(O)₂R^{26a} or N(R²⁷)R²⁸;

R³ represents one or more optional substituents selected from OH, C₁₋₄ alkoxy, C₁₋₆ alkyl (optionally substituted by one or more halo group), or N(R^{29a})R^{29b};

R²⁵, R^{29a} and R^{29b} independently represent H, C₁₋₄ alkyl or C(O)R³⁰;

R²⁶ represents H or C₁₋₄ alkyl;

R^{26a} represents C₁₋₄ alkyl;

R²⁷ and R²⁸ independently represent H, C₁₋₄ alkyl or C(O)R³⁰, or together represent C₃₋₆ alkylene, thus forming a 4- to 7-membered ring, which ring is optionally

substituted, on a carbon atom that is α to the nitrogen atom, with an =O group;

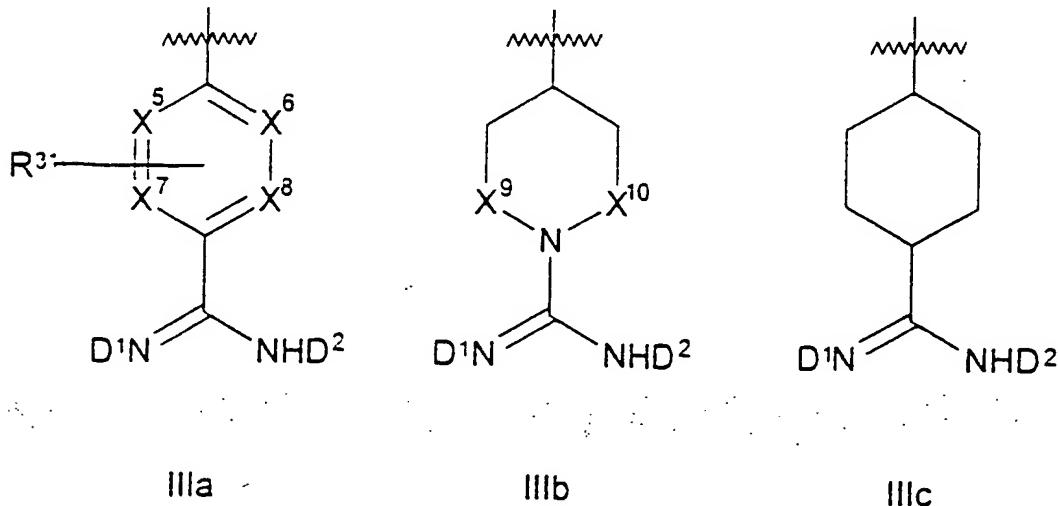
R^{21} , R^{22} , R^{23} , R^{24} and R^{30} independently represent, at each occurrence, H or C_{1-4} alkyl;

Y represents CH_2 , $(CH_2)_2$, $CH = CH$ (which latter group is optionally substituted by C_{1-4} alkyl), $(CH_2)_3$, $CH_2CH=CH$ or $CH=CHCH_2$ (which latter three groups are optionally substituted by C_{1-4} alkyl, methylene, =O or hydroxy);

R^y represents H or C_{1-4} alkyl;

n represents 0, 1, 2, 3 or 4; and

B represents a structural fragment of formula IIIa, IIIb or IIIc



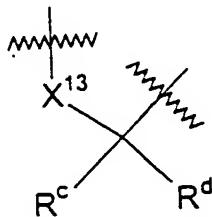
wherein

X^5 , X^6 , X^7 and X^8 independently represent CH, N or N-O;

X^9 and X^{10} independently represent a single bond or CH_2 ;

R^{31} represents an optional substituent selected from halo, C_{1-4} alkyl (which group is optionally substituted by one or more halo group), $N(R^{32})R^{33}$, OR^{34} or SR^{35} ;

R^{32} and R^{33} independently represent H, C₁₋₄ alkyl or C(O)R³⁶;
 R^{34} , R^{35} and R^{36} independently represent H or C₁₋₄ alkyl; and
one of D¹ and D² represents H, and the other represents H, OR^a, NHR^a,
C(=X¹¹)X¹²R^b, or D¹ and D² together represent a structural fragment of formula IVa:-



IVa

R^a represents H or -A⁵[X¹⁴]_n[C(O)]_rR^g;
 R^b represents -A⁵[X¹⁴]_n[C(O)]_rR^g;
 A^5 represents, at each occurrence, a single bond or C₁₋₁₂ alkylene group is optionally interrupted by one or more O, S(O)_m and/or N(R^f) group, and is optionally substituted by one or more of halo, OH, N(H)C(O)R^g, C(O)N(R^g)R^h, C₃₋₇-cycloalkyl (which cycloalkyl group is optionally interrupted by one or more O, S(O)_m and/or N(R^f) group and/or is optionally substituted by one or more substituents selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, halo, =O or =S), Het and C₆₋₁₀ aryl (which aryl and Het groups are themselves optionally substituted by one or more substituents selected from C₁₋₆ alkyl (optionally substituted by one or more halo substituent), C₁₋₆ alkoxy, halo, cyano, C(O)OR^g, C(O)N(R^g)R^h and N(R^f)R^g));
 R^c and R^d both represent H; or one of R^c and R^d represents H or C₁₋₇ alkoxy and the other represents C₁₋₁₇ alkyl (which alkyl group is optionally interrupted by one or more O atoms); or R^c and R^d together represent C₃₋₈ cycloalkyl, which cycloalkyl group

is interrupted by one or more O, S(O)_m and/or N(R^f) group;

R^e represents, at each occurrence, H, C₁₋₁₂ alkyl (which alkyl group is optionally interrupted by one or more O, S(O)_m and/or N(R^f) group, and/or is optionally substituted by one or more substituents selected from halo, OH, N(H)C(O)R^g and C(O)N(R^g)R^h), A⁷-C₃₋₇-cycloalkyl (which cycloalkyl group is optionally interrupted by one or more O, S(O)_m and/or N(R^f) group and/or is substituted by one or more substituents selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, halo, =O and =S), A⁷-C₆₋₁₀ aryl or A⁷-Het (which aryl and Het groups are optionally substituted by one or more substituents selected from C₁₋₆ alkyl (optionally substituted by one or more halo substituent), C₁₋₆ alkoxy, halo, cyano, C(O)OR^g, C(O)N(R^g)R^h and N(R^f)R^g);

A⁷ represents a single bond or C₁₋₇ alkylene (which alkylene group is optionally interrupted by one or more O, S(O)_m and/or N(R^f) group, and/or are optionally substituted by one or more of halo, OH, N(H)COR^g and CON(R^g)R^h);

Het represents, at each occurrence, a five- to ten-membered heteroaryl group, which may be aromatic in character, containing one or more nitrogen, oxygen or sulphur atoms in the ring system;

n and r independently represent 0 or 1;

X¹¹, X¹² and X¹⁴ independently represent O or S;

X¹³ represents O or N(R^f);

R^f represents, at each occurrence, H, C₁₋₄ alkyl or C(O)R^g;

R_g and R^h independently represent, at each occurrence, H or C₁₋₄ alkyl; and

m represents, at each occurrence, 0, 1 or 2;

or a pharmaceutically acceptable salt thereof;

provided that:

(a) ~~A and E do not both represent O or S;~~

(b) ~~E and D do not both represent O or S;~~

(c) ~~when R¹ represents OR^{1d} and X₁ represents C(O)-Z-A¹,~~

~~-Z-CH₂S(O)_m-A²- or -Z-C(O)-Z-A², then A¹ or A² (as appropriate) do not represent a single bond;~~

(f) ~~when X₄ represents CH(R²³), R¹ does not represent OH;~~

(g) (a) when A⁵ represents a single bond, then n and r both represent 0;

(f) (b) when A⁵ represents C₁₋₁₂ alkylene, then n represents 1;

(g) (c) when A⁵ represents -CH₂-, n is 1 and r is 0, then R^e does not represent H;

and

(h) (d) the compound is not:-

(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Pro-Pab;

(R)- or (S)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Pro-Pab;

(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab x HOAc;

(R)- or (S)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab;

1-hydroxy-5-methoxytetralin-1-yl-C(O)-Aze-Pab x HOAc;

1-hydroxy-5,7-dimethyltetralin-1-yl-C(O)-Aze-Pab x HOAc;

1-hydroxy-7-aminotetralin-1-yl-C(O)-Aze-Pab x HOAc;

1-hydroxytetralin-1-yl-C(O)-Aze-Pab x HOAc;

7-methoxytetralin-1-yl-C(O)-Aze-Pab x HOAc;

(R)- or (S)-7-methoxy-1-methyltetralin-1-yl-C(O)-Aze-Pab;

4-hydroxy-6-methoxychroman-4-yl-C(O)-Aze-Pab x OAc;

(S)- or (R)-1-hydroxy-4-methoxyindan-1-yl-C(O)-Aze-Pab;
1-hydroxy-5-methoxytetralin-1-yl-C(O)-Aze-Pab(OH);
(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(OH);
4-hydroxy-6-methoxychroman-4-yl-C(O)-Aze-Pab(OH);
4-hydroxy-6-methoxychroman-4-yl-C(O)-Aze-Pab(OMe);
(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab-
(C(O)OCH₂CCl₃);
(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab-
(C(O)OCH₂CH₃);
7-methoxy-1-allyltetralin-1-yl-C(O)-Aze-Pab x HOAc;
(S)- or (R)-1-hydroxy-7-chlorotetralin-1-yl-C(O)-Pro-Pab;
1-n-propyl-7-methoxytetralin-1-yl-C(O)-Aze-Pab x HOAc;
6-chloro-4-hydroxychroman-4-yl-C(O)-Aze-Pab x HOAc;
4-hydroxychroman-4-yl-C(O)-Aze-Pab x HOAc;
6,8-dichloro-4-hydroxychroman-4-yl-C(O)-Aze-Pab x HOAc;
6-fluoro-4-hydroxychroman-4-yl-C(O)-Aze-Pab x HOAc;
4-hydroxy-6-methylchroman-4-yl-C(O)-Aze-Pab x HOAc;
8-chloro-4-hydroxy-6-methoxychroman-4-yl-C(O)-Aze-Pab x HOAc;
6-chloro-4-hydroxy-8-methylchroman-4-yl-C(O)-Aze-Pab x HOAc;
(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(O-C(O)-i-Pr);
(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(O-C(O)-Et);
(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(O-C(O)-Ch);
(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(O-allyl);

(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(0-Bzl);
(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab-(CO-O-methallyl);
1-hydroxy-7-aminotetralin-1-yl-C(O)-Aze-Pab(OH);
(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-Pab(O-Val);
(S)- or (R)-1-hydroxy-7-methoxytetralin-1-yl-C(O)-Aze-(Me)Pab; or
9-hydroxyfluoren-9-yl-C(O)-Aze-Pab x HOAc.

2 (original). A compound as claimed in Claim 1 wherein R¹ represents OH or C₁₋₄ alkyl (which latter group is optionally substituted by cyano or OH).

3 (canceled).

4 (currently amended). A compound as claimed in claim 1 wherein, when R_x represents a the dotted lines in the structural fragment of formula IIa, then the dotted lines represent bonds, A and E both represent CH and D represents -CH=CH-.

5 (currently amended). A compound as claimed in claim 1 wherein, when R_x represents a structural fragment of formula IIa, X₁ represents optionally unsaturated C₂- or C₃-alkylene, or Z-A³ (in which Z represents O, S(O)_m or N(R²⁵) (in which R²⁵ is as defined above or represents C₁₋₄ alkyl or C(O)R³⁰ and m and R³⁰ are as defined above) and A³ represents C₁₋ or C₂-alkylene (which latter group is optionally unsaturated)).

6 (previously presented). A compound as claimed in claim 1 wherein Y represents CH₂, (CH₂)₂ or (CH₂)₃.

7 (previously presented). A compound as claimed in claim 1 wherein B represents a structural fragment of formula IIIa in which X⁵, X⁶, X⁷ and X⁸ all represent CH.

8 (previously presented). A compound as claimed in claim 1 wherein, when D¹ and D² together represent a structural fragment of formula IVa, in which X¹³ is O, then one of R^c and R^d represents H or C₁₋₇ alkoxy and the other represents C₁₋₇ alkyl.

9 (previously presented). A compound as claimed in claim 1, wherein, when D¹ or D² represents OR^a and R^a represents -A⁵[X¹⁴]_n[C(O)]_rR^e, and

(i) A⁵ is a single bond, then R^e is:-

(1) A⁷-aryl, optionally substituted by one or more halo, C₁₋₆ alkoxy, C₁₋₆ alkyl or halo-C₁₋₆-alkyl substituents; or

(2) H or linear, branched, optionally unsaturated, and/or cyclic, C₁₋₁₂ alkyl, which cyclic alkyl group is optionally interrupted by an O atom and, optionally, a further O atom or S(O)_m group; or when

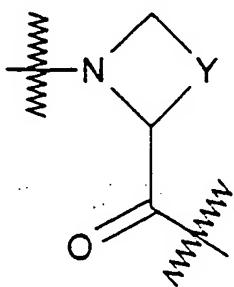
(ii) A⁵ is linear or branched C₁₋₁₂ alkylene, X¹⁴ is O and r is 0, then R^e is C₁₋₃ alkyl or A⁷-aryl, in which A⁷ is a single bond.

10 (previously presented). A compound as claimed in claim 1, wherein, when D¹

or D² represents OR^a, then R^a is H or C₁₋₄ alkyl.

11 (previously presented). A compound as claimed in claim 1, wherein, when D¹ or D² represents -C(=X¹¹)X¹²R^b, in which X¹¹ represents O and X¹² represents O or S, and, in which R^b group, A⁵ represents a single bond then R^e represents optionally unsaturated C₁₋₆ alkyl, A⁷-C₆₋₁₀-aryl (in which A⁷ represents a single bond or C₁₋₂ alkylene, and which A⁷-C₆₋₁₀-aryl group is optionally substituted by one or more halo, C₁₋₄ alkyl and/or C₁₋₄ alkoxy groups), or A⁷-C₃₋₇-cycloalkyl, in which A⁷ represents a single bond or linear or branched C₁₋₇ alkylene, and which cycloalkyl group is optionally substituted by C₁₋₃ alkyl.

12 (previously presented). A compound of formula I, as defined in claim 1, wherein the fragment



is in the S-configuration.

13 (previously presented). A pharmaceutical formulation including a compound as defined in claim 1, or a pharmaceutically acceptable salt thereof, in admixture with a

pharmaceutically acceptable adjuvant, diluent or carrier.

14-20 (canceled).

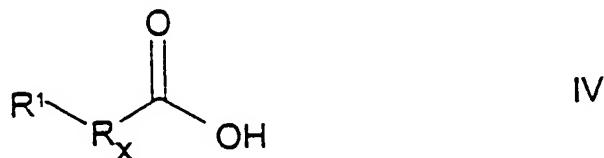
21 (previously presented). A method of treatment of a condition where inhibition of thrombin is required which method comprises administration of a therapeutically effective amount of a compound as defined in claim 1, or a pharmaceutically acceptable salt thereof, to a person suffering from, or susceptible to, such a condition.

22 (original). A method as claimed in Claim 21, wherein the condition is thrombosis.

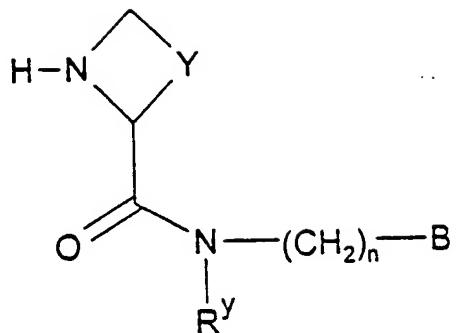
23 (original). A method as claimed in Claim 21, wherein the condition is hypercoagulability in blood and tissues.

24 (original). A process for the preparation of compounds of formula I which comprises:

(i) the coupling of a compound of formula IV,



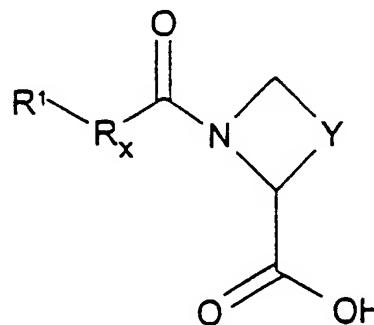
wherein R¹ and R_x are as defined in Claim 1 with a compound of formula V,



V

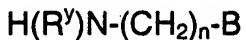
wherein R^y, Y, n and B are as defined in Claim 1;

(ii) the coupling of a compound of formula VI,



VI

wherein R¹, R_x and Y are as defined in Claim 1 with a compound of formula VII,

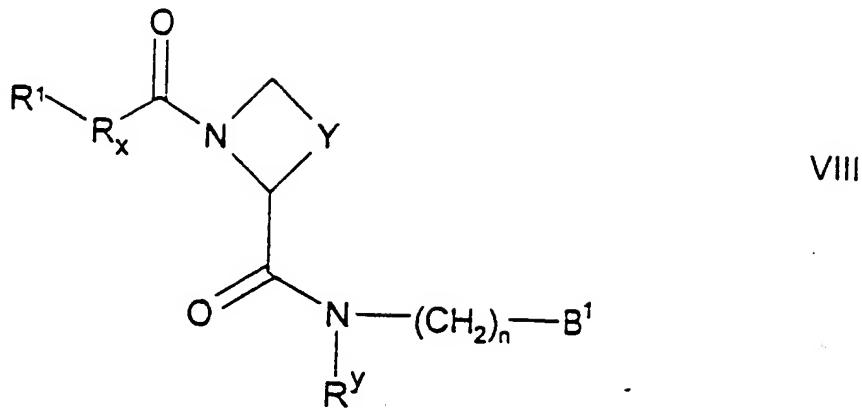


VII

wherein R^y, n and B are as defined in Claim 1;

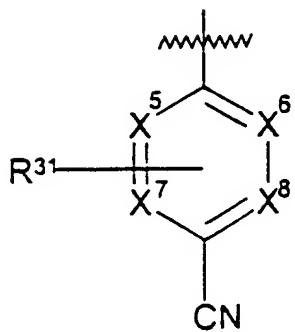
(iii) for compounds of formula I in which D¹ or D² represents OR^a or NHR^a,

reaction of a compound of formula VIII,

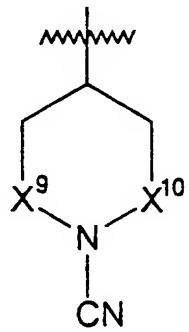


VIII

wherein B^1 represents a structural fragment of formula IIId, IIIe or IIIf



III d



III e



III f

and R^1 , R_x , Y , R^y , n , R^{31} , X^5 , X^6 , X^7 , X^8 , X^9 and X^{10} are as defined in Claim 1 with a compound of formula IX,



wherein X^a represents O or NH and R^a is as defined in Claim 1;

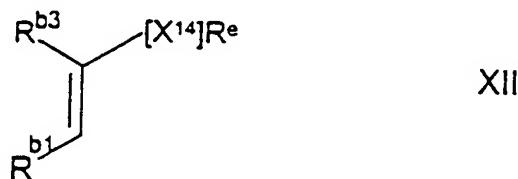
(iv) for compounds of formula I in which D¹ or D² represents OR^a or NHR^a, reaction of a compound of formula I in which D¹ or D² (as appropriate) represents C(O)OR^{b1}, in which R^{b1} represents a protecting group with a compound of formula IX as defined above;

(v) for compounds of formula I in which D¹ or D² represents OR^a or NHR^a, R^a represents -A⁵[X¹⁴]_n[C(O)]_rR^e, in which A⁵ does not represent a single bond, and n represent 1, reaction of a compound of formula I in which D¹ or D² (as appropriate) represents OH or NH₂, with a compound of formula X,



wherein L¹ represents a suitable leaving group, A^{5a} represents A⁵, as defined in Claim 1 except that it does not represent a single bond, and X¹⁴, r and R^e are as defined in Claim 1;

(vi) for compounds of formula I in which D¹ or D² represents OR^a or NHR^a, R^a represents -A⁵[X¹⁴]_n[C(O)]_rR^e, in which A⁵ represents C₂₋₁₂ alkylene, which alkylene group is branched at the carbon atom that is α to the O or N atom of OR^a or NHR^a (as appropriate), and which group is optionally branched at the carbon atom that is β to that atom, n represents 1, r represents 0 and R^e is as defined in Claim 1, reaction of a compound of formula I in which D¹ or D² (as appropriate) represents OH or NH₂, with a compound of formula XI,



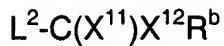
or a geometrical isomer thereof, or a mixture of such geometrical isomers, in which R^{b1} and R^{b3} each represent H or an alkyl group, provided that the total number of carbon atoms provided by R^{b1} and R^{b3} does not exceed 10, and wherein X¹⁴ and R^e are as defined in Claim 1;

(vii) for compounds of formula I in which D¹ or D² represents OR^a or NHR^a, represents -A⁵[X²⁴]_n[C(O)]_rR^e, in which A⁵ represents a single bond, and R^e represents A⁷-C₃₋₆-cycloalkyl, in which A⁷ represents a single bond, and the cycloalkyl group is interrupted by at least one O or S atom, which atom is between the carbon atom at the point of attachment to the O or NH group of OR^a or NHR^a, and a carbon atom that is α to that point of attachment, and which cycloalkyl group is optionally interrupted by one or more O or S(O)_m group and/or optionally substituted by one or more =O group, reaction of a compound of formula I, in which D¹ or D² (as appropriate) represents OH or NH₂, with a compound of formula XII,



wherein X¹⁵ represents O or S and X¹⁶ represents C₁₋₄ alkylene (which alkylene group is optionally interrupted by one or more O or S(O)_m group and/or optionally substituted by one or more =O group);

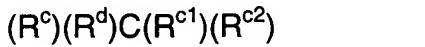
(viii) for compounds of formula I in which D¹ or D² represents C(X¹¹)X¹²R^b, reaction of a compound of formula I in which D¹ and D² both represent H with a compound of formula XIII,



XIII

wherein L^2 represents a suitable leaving group, and X^{11} , X^{12} and R^b are as defined in Claim 1;

(ix) for compounds of formula I in which D^1 and D^2 together represent a structural fragment of formula IVa, reaction of a corresponding compound of formula I in which D^1 or D^2 represents OH or NHR^f (in which R^f is as defined in Claim 1), with a compound of formula XV,



XV

wherein R^{c1} and R^{c2} both represent $-OR^{c3}$, in which R^{c3} represents C_{1-3} alkyl, or together represent $=O$, and R^c and R^d are as defined in Claim 1;

(x) for compounds of formula I in which one or more of X^5 , X^6 , X^7 and X^8 represent N-O, oxidation of a corresponding compound of formula I in which X^5 , X^6 , X^7 and/or X^8 (as appropriate) represent(s) N; or

(xi) for compounds of formula I in which any one of Z , X_1 , R^2 , R^4 , A^5 , A^7 , R^c , R^d and/or R^e comprises or includes a (O) or a $S(O)_2$ group, oxidation of a corresponding compound of formula I (or a compound corresponding to a compound of formula I) wherein Z , X_1 , R^2 , R^4 , A^5 , A^7 , R^c , R^d and/or R^e (as appropriate) comprise(s) or include(s) a S group;

(xii) for compounds of formula I in which D^1 and D^2 both represent H, removal of a OR^a , NHR^a or $C(=X^{11})X^{12}R^b$ group (in which R^a , R^b , X^{11} and X^{12} are as defined in Claim 1), or removal of a structural fragment of formula IVa as defined in Claim 1, from a corresponding compound of formula I; or

(xiii) introduction and/or interconversion of a substituent on an aromatic and/or

INGHARDT et al
Appl. No. 10/815,954
June 30, 2005

non-aromatic, carbocyclic and/or heterocyclic ring in a corresponding compound of formula I.